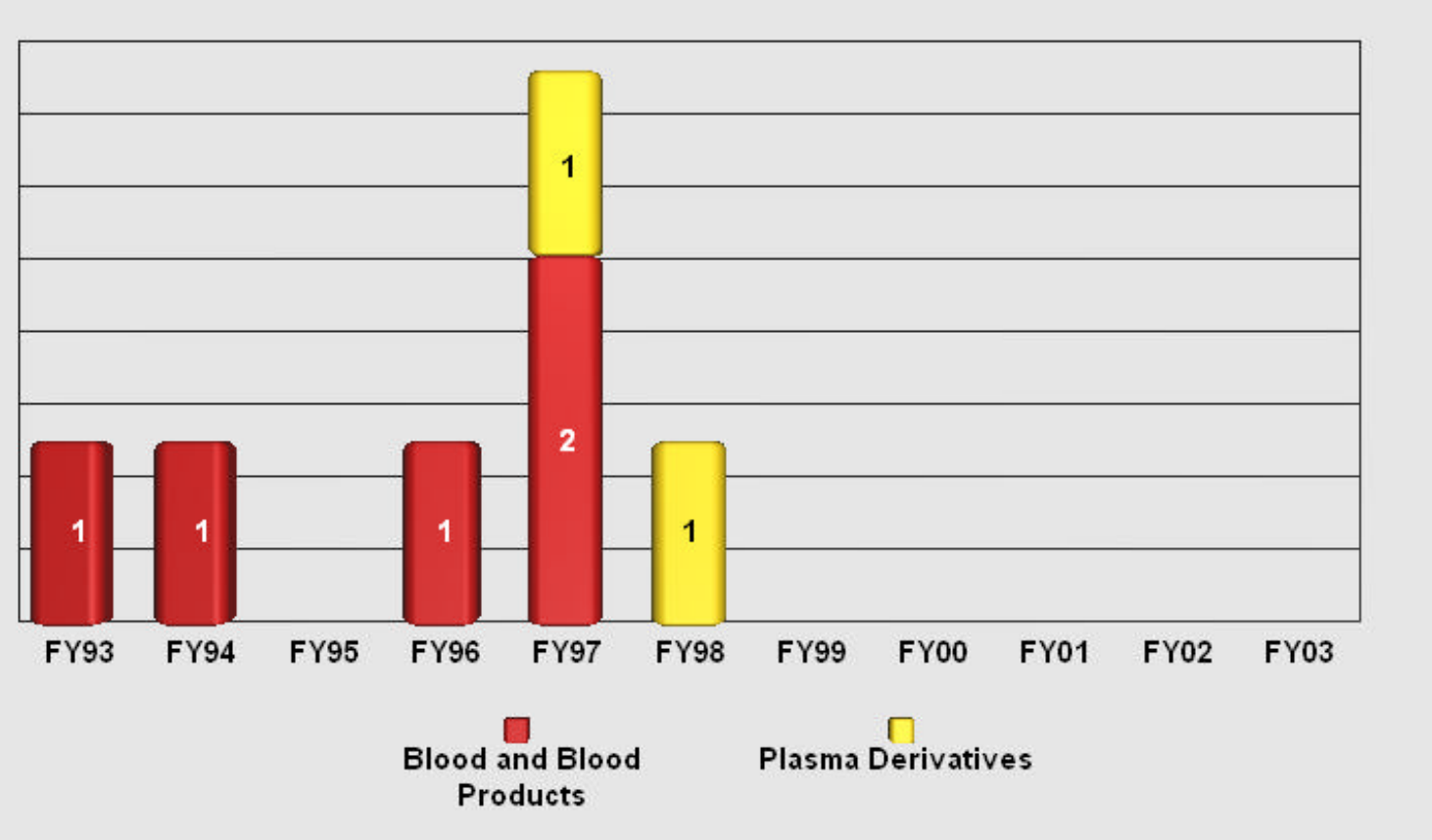
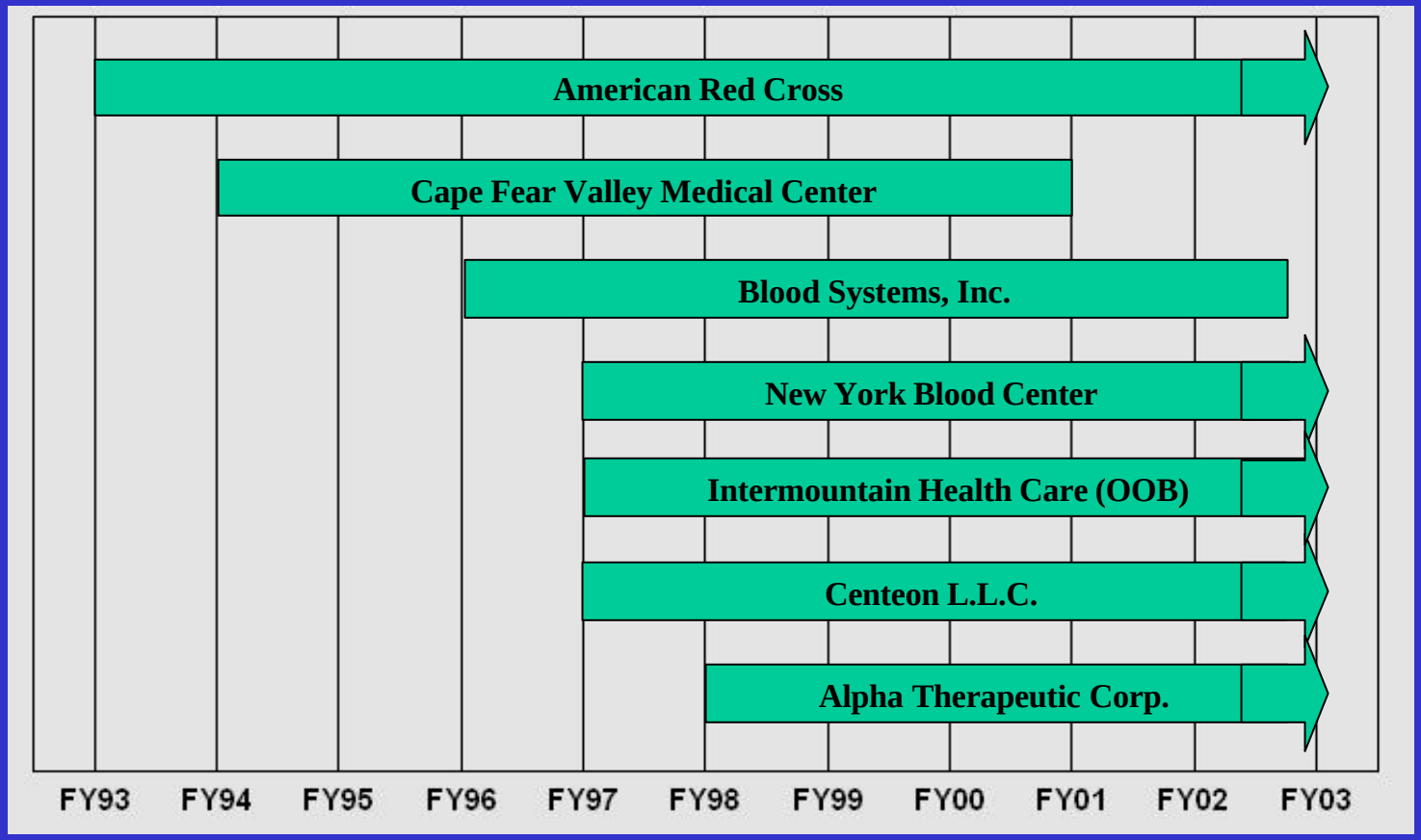
Injunctions
Blood and Plasma



Injunctions
Blood and Plasma



What Do These Administrative/ Judicial Action Numbers Mean?

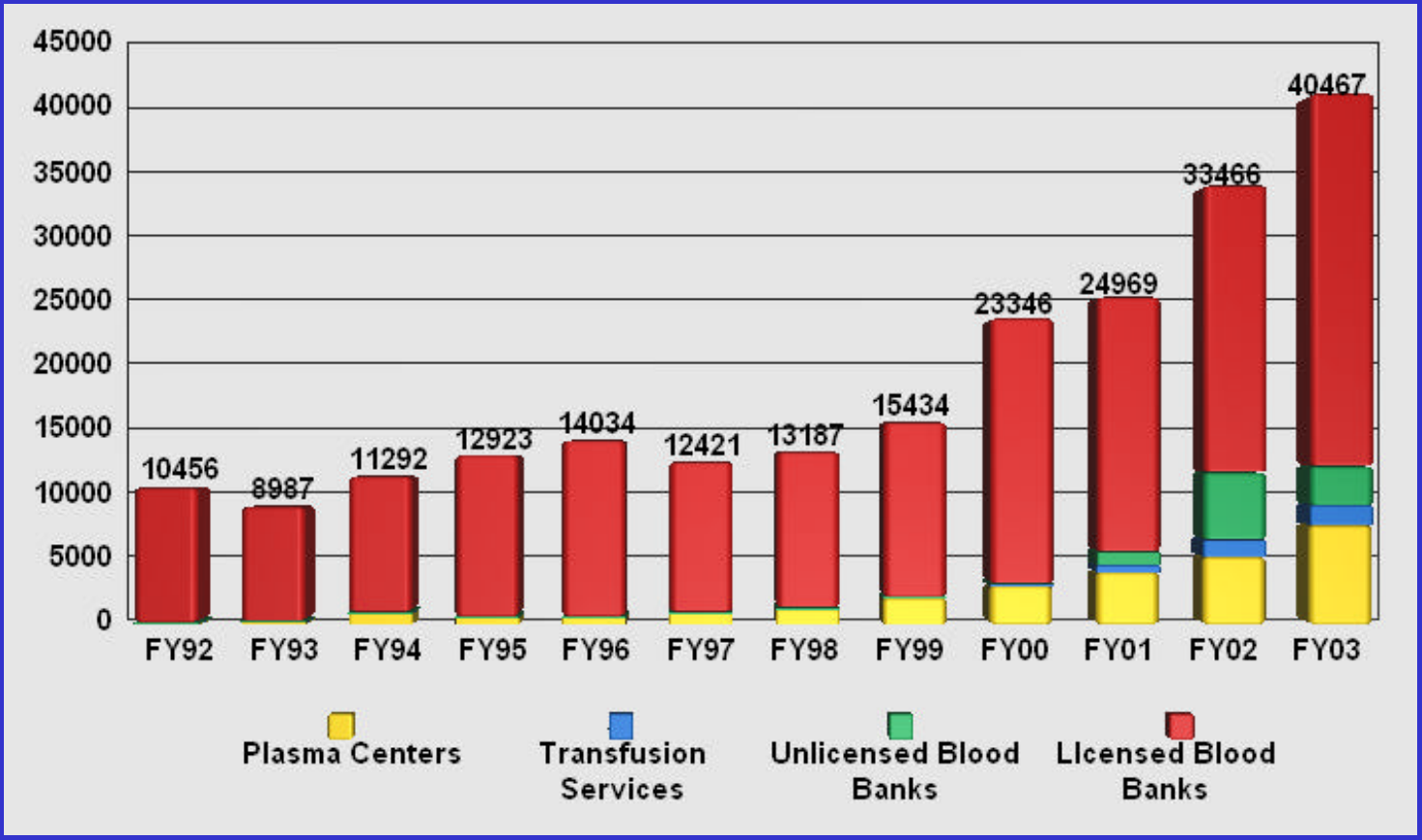
- Administrative and judicial actions are generally decreasing – suggests improvement, at least with regard to severity of deviations
- Other factors? (e.g., resources, quality approach, reviews)
- Warning Letters not issued to 50-55% of blood industry, which is operating under consent decree

Biological Product Deviation Reports

- 21 CFR 606.171
- Reporting required by:
  - Licensed and registered firms
  - Transfusion services in control of product when deviation occurred
- Submit reports within 45 days of discovery of reportable event

Biological Product Deviation Reports

Blood and Source Plasma

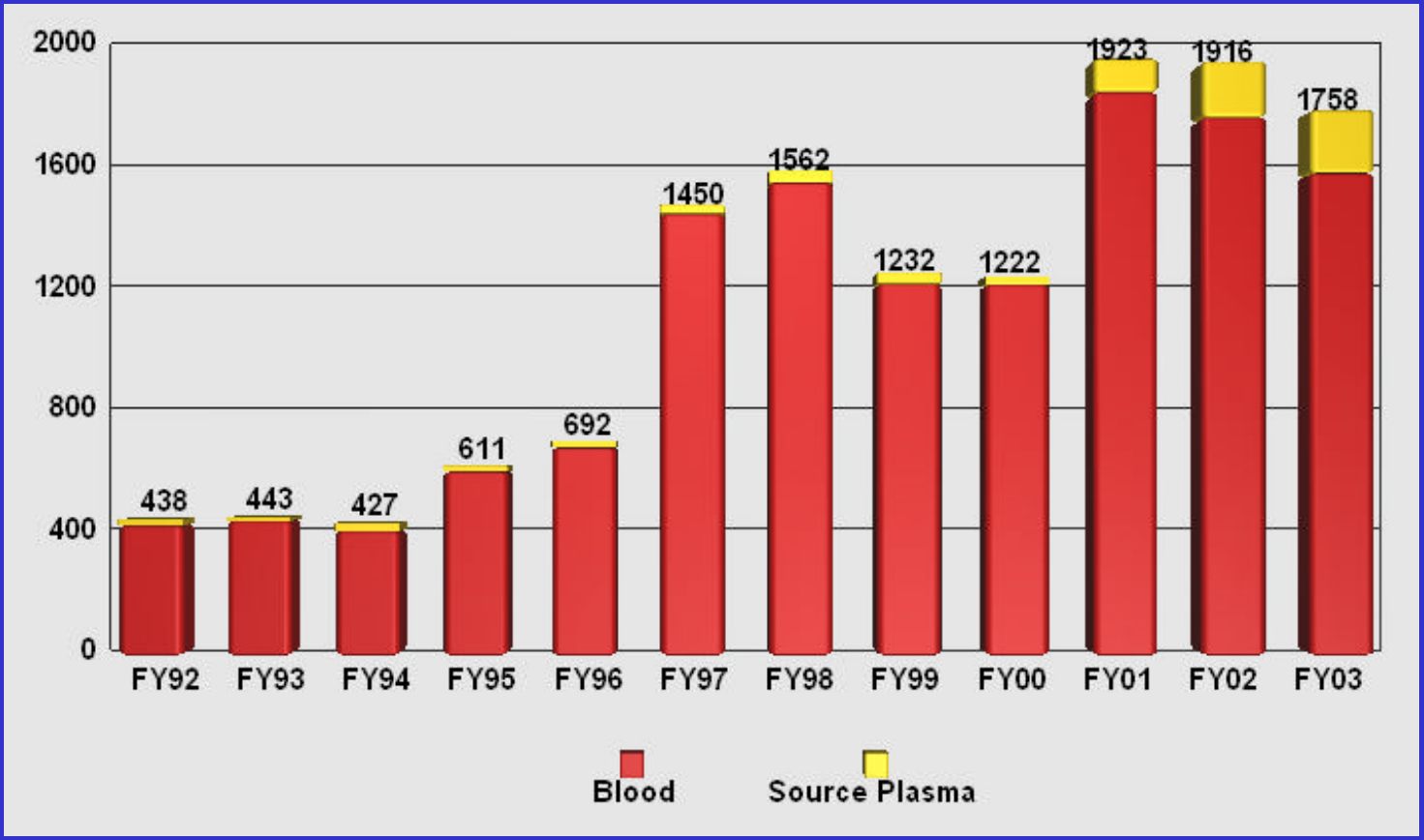


Recalls

- 21 CFR Part 7 Subpart C
- Voluntary action in lieu of FDA-initiated court action for product removal or correction
- Voluntary action to carry out firm's responsibility to protect the public health with respect to its products
- Classified as Class I, Class II, or Class III

Recalls Classified

Blood and Source Plasma



What Do These BPDR/Recall Numbers Mean?

- BPDRs are increasing
  - Additional establishments required to report → more establishments reporting
  - CBER's outreach efforts (training/speeches/guidance)
  - Firms' efforts
- Recalls up in FY's 01 and 02, slight decrease in FY 03
- Increased focus on investigations as result of improved focus on deviations

Systems-Based Inspections – Risk-Based Strategies

- Traditional Inspection Approach
- Systems-Based Inspections
- New Compliance Program Guide
- Five Blood Systems - Five Layers of Safety
- Inspection Specifics
  - Frequency
  - Levels

“Traditional” Blood/Plasma Inspections

- Previous Inspection Program last revised in 1999
- Audit approach
- Comprehensive inspection biennially
- All critical areas covered in detail

Critical Areas

"Traditional" Inspections

- Computer Systems
- Training/Personnel
- Donor Suitability
- Donor Deferral
- Testing
- Quarantine
- Quality Assurance
- Lookback
- Storage/Shipping/Distribution (Source Plasma)

What Are Systems-Based Inspections?

- Risk management approach
- Developed jointly by CBER and Office of Regulatory Affairs
- Focuses on operating systems found in most blood establishments
- Provides method to determine level of inspectional coverage and resources appropriate for each inspection

Why Systems-Based Inspections?

- Agency initiative
- Builds on knowledge gained from previous inspections and scientific developments
- More focused inspections
- Best use of resources
- Optimizes level of effort necessary to determine compliance

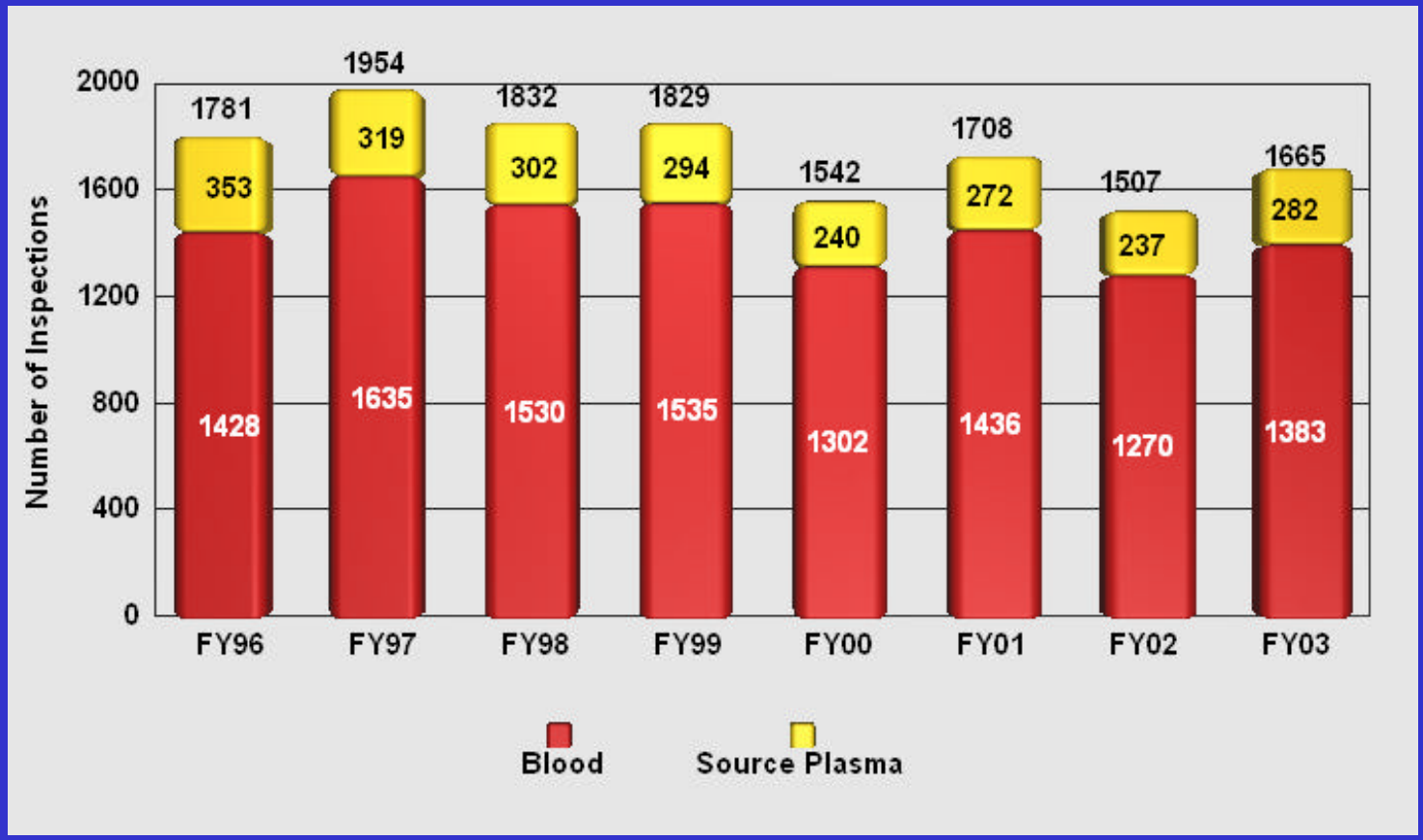
Perspective on Inspections

- Numbers of inspections

  vs.

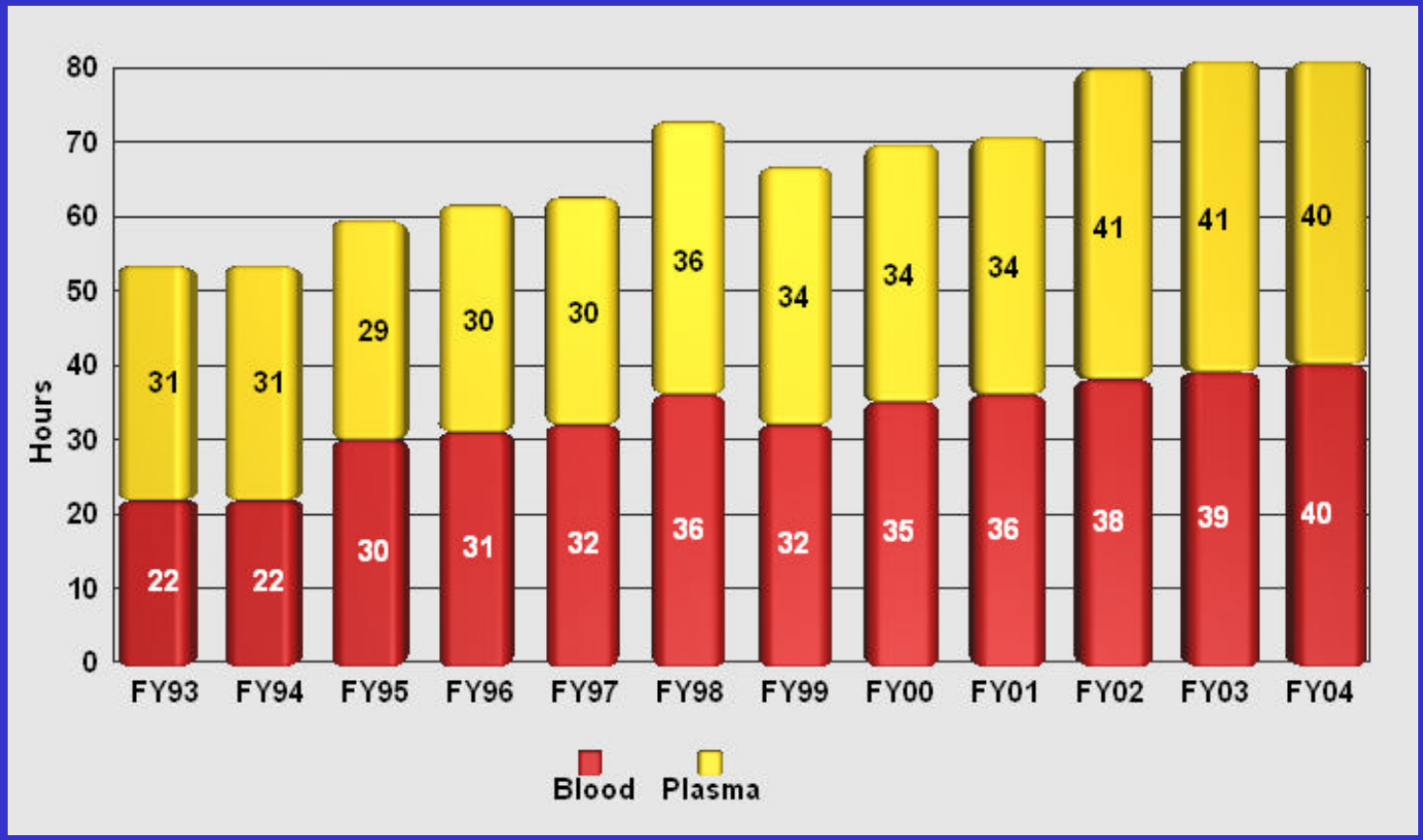
- Time spent on inspections

Inspection Numbers



Inspection Times

(Based on FDA Workplan Inspection Modules*)



* Hours planned for preparation, inspection, and writing report

Systems-Based Inspections

- Compliance Program Guide: 7342.001 - "Inspection of Licensed and Unlicensed Blood Banks, Brokers, Reference Laboratories, and Contractors
  - Issued July 1, 2003
  - Implemented September 1, 2003
  - http://www.fda.gov/cber/cpg/cpg.htm
- Source Plasma CPG will be systems-based next revision

Compliance Program Guide

- Objective is to assure products are safe, pure, effective, and appropriately labeled
- To help assure, through inspections, that manufacturers are making products that:
  - Meet the standards in the regulations
  - Meet any additional conditions of licensure incorporated in the Biologic License Application (BLA)

Compliance Program Guide
continued

- Provides regulatory and administrative guidance to FDA Investigators
- Provides information necessary to evaluate the quality of products
- Includes information on how to address non-compliance with applicable regulations

Compliance Program Guide
continued

- Applies to:
  - Blood Banks (domestic and foreign)
  - Blood and/or Plasma Brokers
  - Component Preparation Facilities
  - Contractors
  - Distribution Centers or Depots
  - Donor/Collection Centers
  - Hospital Transfusion Services
  - Indian Health Service Hospitals
  - Military Blood Banks and Transfusion Services
  - Testing Laboratories
  - Veteran’s Health Administration Medical Centers
  - Other blood establishments

Traditional Five Layers of Blood Safety

- Donor Screening
- Donor Deferral
- Product Testing
- Quarantining
- Monitoring and Investigating Problems

Donor Screening

- Procedures to identify donors who have defined risk factor(s) for communicable disease(s) or who are otherwise unsuitable to donate

Donor Deferral

- Procedures to identify unsuitable donors and prevent the distribution of blood products collected from these donors

Product Testing

- Procedures to properly test blood for required infectious diseases and antigens and antibodies that may cause a hemolytic transfusion reaction

Quarantining

- Procedures to assure that blood products are quarantined until all tests and control procedures are acceptable and unsuitable products are removed from inventory

Monitoring and Investigating Problems

- Procedures to identify system problems, biologic product deviations, and blood donor and recipient adverse reactions and to assure that adequate corrective action is implemented

Five Blood Systems

1. Quality Assurance
2. Donor (Suitability) Eligibility
3. Product Testing
4. Quarantine/Inventory Management
5. Production and Processing

Five Blood Systems
continued

- All five systems may not be found in every establishment
- Inspection will focus on the systems that are present

Critical Areas of Each System

- Inspection will include in-depth audit of critical areas in each system
- Identified through risk assessment
- May affect safety and quality of product if system controls are inadequate or not functioning correctly

System Critical Areas

- Standard Operating Procedures
- Personnel/Training
- Facilities
- Equipment Calibration and Maintenance
- Records

Relationship Between Layers and Systems

Layers of Safety	Blood Systems
Donor Screening	Donor Eligibility Quality Assurance
Donor Deferral	Donor Eligibility Quality Assurance
Product Testing	Product Testing Quality Assurance Production and Processing
Quarantining	Quarantining/Inventory Management Quality Assurance Production and Processing
Monitoring and Investigating Problems	Quality Assurance Production and Processing

Frequency of Inspections

- Routinely conducted biennially
  - Statutory obligation
- Exceptions to biennial inspections:
  - Firms under Consent Decree
  - Newly licensed or registered establishment
    - Inspected within first year of operation
  - Compliance follow-up inspections
    - Verification of implementation of corrective action following regulatory action

Levels of Inspection

- Level I
  - All five systems
  - If firm has three systems or less
  - Comprehensive evaluation of the establishment's compliance
- Level II
  - Three systems
  - Streamlined evaluation of establishment's compliance

Level I Inspections

- Comprehensive evaluation of compliance
- Apply to:
  - Initial inspection of firm
  - Firms with history of fluctuating compliance
  - Compliance follow-up inspections
  - Firm that implemented significant changes since prior inspection
  - Firms that perform viral marker testing
  - Surveillance inspection at District's discretion
  - Firms with two previous inspections under Level II

Level II Inspections

- CGMP surveillance or compliance inspections
- Provides verification of continued compliance
- Always includes
  - Quality Assurance
  - Donor (Suitability) Eligibility
  - Third system that is rotated

Level II Inspections
continued

- Determination of third system
  - Review of firm's file
  - Evaluation of inspectional history
  - Assessment of BPDRs, recalls, etc.
- Level II inspections may require limited coverage of other systems
  - e.g., investigation and correction of deviations
- Must include inspection of significant changes to manufacturing processes or new products since last inspection

Level II Inspections
continued

- Applied when:
  - Firms have satisfactory compliance history
    - Three successive NAI/VAI inspections
  - One of two previous inspections was Level I
  - Inspection preparation reveals no trends
- Finding significant objectionable conditions may prompt change to Level I

Exceptions to Systems-Based Inspections

- Not applied to firms under Consent Decree
- Not applied to pre-license and pre-approval inspections

How Will Systems-Based Inspections Affect You?

- Your responsibility will not change
- Still looking for same high standard of performance
- Ability to focus resources during an inspection

Possible Outcomes of Systems-Based Inspections

- Shorter inspections
- More time for FDA to focus on high risk or problem areas/facilities (resource allocation)
- More industry focus on critical systems

Conclusions

- There are always new issues/events coming along that present challenges (some in your control, some not)
- Numbers presented today are encouraging
- Still more work to do
- Too many firms under consent decree

Information and Contacts

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